AF/1600

TRANSMITTAL OF APPEAL BRIEF

Docket No. **420522000100**

In re Application of: Tracy D. WILKINS, et al

Application No.	Filing Date	Examiner	Group Art Unit
09/545,772	April 10, 2000	V. Ford	1645

Invention: RECOMBINANT TOXIN A PROTEIN CARRIER FOR POLYSACCHARIDE CONJUGATE VACCINES

TO THE COMMISSIONER OF PATENTS:

Transmitted herewith in triplicate is the Appeal Brief in this application, with respect to the Notice of Appeal filed: December 12, 2002 .

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Dated: April 10, 2003

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sd-141588

PATENT
Docket No. 420522000100

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In the application of:

Tracy D. WILKINS, *et al.*

Serial No.: 09/545,772

Filing Date: 10 April 2000

For: RECOMBINANT TOXIN A PROTEIN CARRIER FOR POLYSACCHARIDE CONJUGATE VACCINES

Examiner: Vanessa L. Ford

Group Art Unit: 1645

BRIEF ON APPEAL

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

A Notice of Appeal was filed in this action on 12 December 2002, thus setting a date for filing of the Brief of 12 February 2003. A two month extension of time is filed herewith thus extending the time for response until 12 April 2003. This is an Appeal from the final rejection of claims 1, 3, 6, 13-15, 19-20, 23-26, 28-31, 33, 36-39, 62 and 63 in the above-referenced application. In accordance with 37 C.F.R. § 1.192, this Brief, along with the Appendix, is filed **in triplicate** and is accompanied by the required fee.

sd-129063

1. Real Parties in Interest

The real parties in interest in this appeal are the National Institutes of Health by virtue of an assignment recorded in the U.S. Patent and Trademark Office on December 20, 2002, Reel/Frame: 013312/0882, and TechLab, Inc. by virtue of an assignment recorded in the U.S. Patent and Trademark Office on June 25, 2002, Reel/Frame: 013054/0362.

2. Related Appeals and Interferences

There are no other Appeals or Interferences known to the appellants, the appellants' legal representative, or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the present pending appeal.

3. Status of Claims

Claims 1-61 were originally filed. Original claims 2, 4-5, 7-8, 9-12, 16-18, 21-22, 27, 32, 34-35, and 40-60 were canceled in the Amendment under 37 C.F.R. § 1.111, filed August 20, 2001 (claims 40-60), in the Amendment under 37 C.F.R. § 1.111, filed April 26, 2002 (claims 9-12, 16-18, 21-22, 27, 32, and 34-35) and in the Amendment under 37 C.F.R. § 1.116, filed October 15, 2002, (claims 2, 4-5 and 7-8) without prejudice to appellants' right to pursue the subject matter of these claims in subsequent applications. Claims 62-66 were added in the Amendment under 37 C.F.R. § 1.111, filed April 26, 2002. Claims 64-66, directed to methods of using the immunogenic composition of claims 1, 36 or 37, were withdrawn as directed to a non-elected invention according to the Advisory Action, mailed November 26, 2002. Pending claims 1, 3, 6, 13-15, 19-20, 23-26, 28-31, 33, 36-39, 62 and 63 have been finally rejected. The claims involved in this appeal, claims 1, 3, 6, 13-15, 19-20, 23-26, 28-31, 33, 36-39, 62 and 63, as well as withdrawn claims 64-66, which should be rejoined, are presented in the appendix attached hereto as Exhibit A.

4. **Status of Amendments**

The Amendment filed by the appellants under 37 C.F.R. §1.116 on October 15, 2002 including amendments to claims 1, 14, and 64-66 have been entered according to the Advisory Action mailed November 26, 2002.

5. **Summary of the Inventions**

The invention is directed to immunogenic compositions where the immunogen of interest is specifically a polysaccharide and where the polysaccharide is administered with a particularly effective carrier, namely, the repeating unit of the *C. difficile* toxin A (rARU). Please see the present specification on page 8, line 28, and page 9, lines 6-7. Appellants have demonstrated the effectiveness of this carrier in the present application, in Example 4 with respect to *Shigella flexneri, E. coli,* and *Pneumococcus*. The vaccines are administered by injection, and the claimed composition is formulated as such, as set forth in Example 4. See page 21, lines 6-10. This formulation is in contrast to the Thomas document discussed below which describes the adjuvant effects of toxin A or GST-ARU in an administration route which addresses the mucosa directly. Please see Thomas, *e.g.,* Examples I, II, IVB, and V.

"One of the problems encountered in immunizing subjects for protection against infection where the antigen is a polysaccharide is that such polysaccharides may not be sufficiently immunogenic alone to elicit an immune response." Therefore, they require the use of an immunogenic carrier to aid in eliciting an immune response. Such carriers as pertussis toxin, diphtheria toxin, and tetanus toxin have been frequently used; however, overuse of these carriers results in the inability of the subject to later respond to administration of a vaccine for protection against these microorganisms. Please see page 4, lines 8-21 of the present specification. Thus, for example, if tetanus toxoid is used as a carrier, there is a possibility that the subject will no

longer respond to immunization against tetanus. Therefore, it is desirable to provide a variety of carriers in order to prevent overuse of a single type, as provided by the present invention.

6. Issues

a) Whether *prima facia* anticipation under 35 U.S.C. § 102(e) has been established for claims 1, 3, 6, 13-15, 19-20, 25-26, 28-29, 36-39, 62 and 63 based on U.S. Patent No. 5,919,463 issued to Thomas *et al.* (Thomas) absent a disclosure therein to a polysaccharide component not characteristic of *C. difficile* as claimed and absent a disclosure of the use of rARU as an adjuvant for eliciting responses to the polysaccharide in a formulation for injection.

b) Whether *prima facia* obviousness under 35 U.S.C. § 103 has been established for

1) claims 1, 3, 6, 13-15, 19-20, 23-24, 36-39 and 63 based on Thomas in view of Schneerson *et al.* (Schneerson);

2) claims 1, 3, 6, 13-15, 19-20, 25-26, 36-39, and 63 based on Thomas in view of Taylor *et al.* (Taylor);

3) claims 1, 3, 6, 13-15, 19-20, 28-29, 36-39 and 63 based on Thomas in view of Devi *et al.* (Devi); and

4) claims 1, 3, 6, 13-15, 19, 30-31, 33, 36-39 and 63 based on Thomas in view of Fattom, *et al.* (Fattom); absent a motivation to substitute Thomas' protein antigens for mucosal administration with each of Schneerson's, Taylor's, Devi's, or Fattom's polysaccharides formulated for injection, wherein rARU is not disclosed as a carrier for the polysaccharide antigen in a formulation for injection.

7. Grouping of Claims

The claims for each ground of rejection stand and fall together.

8. Argument

a) Thomas Does Not Anticipate the Present Claims as Rejected.

The main issue is whether the claimed composition directed to a polysaccharide component that is not characteristic of *C. difficile* and rARU formulated for injection, is anticipated by Thomas' disclosure of a mucosal formulation containing "any" of countless antigens that may be derived from *C. difficile*, wherein rARU is not disclosed as a carrier in a formulation for injection. Appellants respectfully submit that a *prima facie* case of anticipation has not been established because Thomas fails to disclose the polysaccharide component as claimed, and fails to disclose rARU as a carrier as a formulation for injection.

1) Thomas Does Not Disclose All Claim Limitations

The Examiner alleges that Thomas' generic disclosure of "any" antigen anticipates the particular antigen as claimed, namely polysaccharides. It is well-settled that "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Thomas does not disclose details of the antigen that are in as complete detail as the claimed polysaccharide antigen. Thus, *prima facie* anticipation has not been established for these claims.

In addition, the Examiner's reasoning is not in line with the reasoning in various chemical formula cases. For example, in *In re Arkley*, 172 USPQ 524 (CCPA 1972), the court concludes that a broad disclosure of a chemical formula that is estimated to contain over 230,000 compounds does not anticipate a narrower species encompassed within the genus. *Id* at 525-526. Similarly in the present application, it is respectfully submitted that the broad genus of antigens that contains thousands of members, does not anticipate the narrower species of polysaccharides.

In re Petering, 301 F.2d 676, 133 USPQ 275 (CCPA 1962), stands for the proposition that one may look to a limited class of preferred species for anticipating disclosure of a compound or compounds. It is undisputed that polysaccharides are not specifically disclosed in Thomas, but rather the Examiner repeatedly relies on the generic disclosure of "any" antigen as a basis for the disclosure of a specific antigen, that is the polysaccharides as claimed. The genus "antigen" is not sufficiently limited or well-delineated to encompass polysaccharides. If one looks to the preferred embodiments as suggested in *Petering* to determine which compounds can be anticipated, one will find that Thomas envisions antigens that are proteins such as urease or ovalbumin, or that contain polypeptides such as GST. Please see, *e.g.* Thomas, column 3, lines 36-37 and Example IV. It is respectfully submitted that only by looking at the present claims using impermissible hindsight was the Examiner capable of arriving at polysaccharides as claimed. No disclosure or suggestion of polysaccharides is found in Thomas, and thus Thomas does not disclose a limited class of antigens that may be used to find anticipation.

Further, even if for the sake of argument polysaccharides were disclosed in Thomas, Thomas does not disclose the claimed polysaccharides, or any other antigen for that matter, that are not characteristic of *C. difficile* as claimed. In contrast, Thomas teaches antigens that may be derived from *C. difficile*, and thus may be characteristic thereof. Please see Thomas, column 2, lines 63-64.

Further, the *Arkley* court stated that in order for the anticipation rejection to have been proper the cited reference

> must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference (emphasis in original).

The Examiner's reasoning does not comport with the court's reasoning in *Arkley* with respect to the disclosure of rARU and a formulation for injection as claimed. With regard to rARU, Thomas does not disclose or suggest the use of rARU as an adjuvant to elicit responses to polysaccharide antigens. Similarly as discussed above with respect polysaccharides, the use of rARU as an adjuvant is not sufficiently limited or well-delineated to encompass the specific combination of polysaccharides and rARU. If one looks to the preferred embodiments as instructed in *Petering* to determine which combinations can be anticipated, one will find that Thomas discloses that ARU is used as a fusion protein with GST in Example IVA and is used as an antigen (please see column 12, left side of Table 4) or the GST-ARU combination is used as an adjuvant in Example IVB. rARU is not used as an adjuvant in this or other examples. In other words, the Examiner must pick, choose, and combine various disclosures within Thomas not directly related to each other, in order to arrive at the claimed invention. Such "picking, choosing and combining various disclosures" is contrary to the court's reasoning in *Arkley*. Thus, Thomas does not disclose the claimed combination, and thus does not anticipate the claimed invention.

With regard to the claimed composition as formulated for injection, even if for the sake of argument, Thomas disclosed polysaccharides, Thomas only discloses *C. difficile* adjuvants in the context only of vaccines that are designed for administration to the mucosa. Please see, *e.g.*, Thomas, column 1, lines 34-37, Examples I and II (vaccines are administered intranasally), Example IVA (*C. difficile's* Toxin A's repeating units are coupled to GST as a fusion protein which is an antigen and not an adjuvant as shown in Table 4, left column, but rather used in combination with an adjuvant as shown in Table 4, middle column), Example IVB (vaccine is administered intranasally) and Example V (vaccine is administered to vaginal and rectal mucosal

surfaces). Again, contrary to *Arkley,* the Examiner must pick, choose, and combine various disclosures within Thomas not directly related to each other, in order to arrive at the claimed invention. Thomas does not describe injecting compositions where a *C. difficile* derived protein is an adjuvant, and thus there is no anticipation.

As there was no showing of all of the elements of the present claims as described above, *prima facie* anticipation has not been established.

2) Burden Unfairly Shifted to Appellants

In the Advisory Action mailed November 6, 2002, the Examiner stated for the first time her position as: "there is nothing [in] the record to show why the immunogenic composition of the reference is not the same as the claimed immunogenic composition." By advancing her position as such, the Examiner appears to suggest that the burden is not on her to show that Thomas describes each element of the claim, but rather it is the appellants' burden to show why Thomas does not. As a *prima facia* case of anticipation has not been established as argued above, it is respectfully submitted that such burden shifting is premature and the burden is with the Office first to establish that the polysaccharide antigen is sufficiently limited or well delineated by Thomas' genus of antigens which are preferably proteins or polypeptides, before the appellants must rebut such a showing.

To conclude, as Thomas does not disclose a composition formulated for injection comprising polysaccharides that are not characteristic of *C. difficile*, in combination with rARU as claimed, a *prima facie* case of anticipation has not been established, and reversal of this rejection is respectfully requested.

b) Thomas in Combination with the Secondary References Does Not Render Obvious Present Claims

In the four obviousness rejections outlined in the Issues section above, Thomas is combined with each of four secondary references that independently discloses the use of particular polysaccharides in a formulation for injection. Therefore, the following arguments are made based on these similarities. The above arguments with respect to anticipation, to the extent that they are applicable to the obviousness rejections, are incorporated here by reference.

None of the secondary references that are combined with Thomas overcomes the deficiencies that Thomas does not disclose or suggest the species of a polysaccharide antigen, and does not disclose the species of rARU to be used with a polysaccharide in a composition formulated for injection.

First, it is well settled that there must be more than mere disclosure of a species in a secondary reference to arrive at the claimed invention. Rather there has to be a motivation in the references themselves to select the species to arrive at the claimed invention. Please see *In re Jones*, 958 F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); and *In re Baird*, 16 F3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994). As discussed above Thomas does not direct a skilled artisan to select polysaccharides as the antigen, nor does Thomas direct a skilled artisan to select the species of rARU to be used as a carrier with the polysaccharide antigen. Moreover, Thomas does not direct a skilled artisan to select a composition formulated for injection comprising a polysaccharide and rARU. It is respectfully submitted that it is only by the benefit of looking at the appellants' claims that one could choose a polysaccharide, when the whole of Thomas' disclosure directs one to select protein antigens as discussed above. It is also respectfully submitted that it is only by the benefit of looking at the appellants' claims that one could select rARU derived from the repeat units of *C. difficile* from Thomas' genus of toxins from any

species of the bacterium Colostridium to be used with such polysaccharide. It is further only by the benefit of appellants' claims that one could select a composition formulated for injection from Thomas' genus of formulations, when, at best, Thomas leads one to select compositions related to Toxin A of *C. difficile* only formulated for mucosal administration. Using impermissible hindsight, however, is not the basis upon which obviousness properly is established.

In the Advisory Action mailed November 26, 2002, the Examiner alleges in the sentence bridging pages 7-8 that "Thomas Jr. *et al.* teach...*Escherichia coli, Shingella and Neisseria gonorrhoeae* which contain polysaccharide antigens (columns 2-3)." However it is respectfully submitted that Thomas does not even mention polysaccharides, but rather specifically discloses particular proteins or polypeptides as described above, and thus one is not motivated to select polysaccharides from the genus of antigens disclosed in Thomas.

In the Advisory Action mailed November 26, 2002, the Examiner also alleges on page 8 that "Thomas Jr. *et al.* teach that the compositions of the invention may also be administered by parenteral, intravenous, subcutaneous, intraperitoneal or intramuscular routes (column 3)." Again, Thomas does not lead one to select the species of a composition formulated for injection as claimed. Rather, hindsight is used because in the instances where Thomas discloses the use of a *C. difficile* toxin or derivative as an adjuvant (and not as part of an antigen), in each and every instance it is part of a mucosal formulation. Thus, one is not led to select the species of a composition formulated for injection, when Thomas clearly only leads the skilled artisan to mucosal formulations when *C. difficile* toxins or derivatives are used as an adjuvant.

In the Advisory Action mailed November 26, 2002, the Examiner further alleges on page 8 that "Thomas Jr. *et al.* teach...[that] GST-ARU was used as an adjuvant (column 13)

...[and thus] teach the use of ARU as an adjuvant." This analysis is misplaced based on two grounds. First, the GST-ARU adjuvant is used only in the context of intranasal administration (please see Thomas, column 12, lines 64-67), and second, ARU is used in the context of a fusion protein with GST along with a protein antigen, ovalbumin. Therefore, in order for a skilled artisan to select ARU as an adjuvant in an injection formulation with a polysaccharide as claimed, at a minimum, the artisan first would have to be motivated to modify the mucosal formulation to arrive at an injection formulation, and second would have to be motivated to modify the rARU/protein *adjuvant* to arrive at a rARU/polysaccharide immunogenic composition as claimed. As the Examiner has not provided motivation for both of such modifications, this illustration precisely demonstrates appellants' point that the present claims have been used impermissibly as a guide to pick and choose each species found in various contexts or not found with specificity in Thomas to arrive at the claimed invention.

None of the cited secondary references overcomes these deficiencies. Each of the secondary references discloses a polysaccharide derived from a particular organism used as a basis for rejection of particular claims. For example, Schneerson discloses a conjugate vaccine composed of serotype 14 *S. Pneumoniae* capsular polysaccharide bound to pertussis toxin, and present claims 23-24 require that the pathogenic microorganism is *S. Pneumoniae*. Taylor describes polysaccharide conjugates of *Shigella* polysaccharides with bacterial toxoids, and present claims 25-26 are directed to *Shigella*. Devi describes conjugates of capsular polysaccharides from *N. meningitides* and *E. coli* with tetanus toxoid, and present claims 28 and 29 are directed *to N. meningitides* and *E. coli* respectively. Finally, Fattom describes a conjugate of capsular polysaccharides from *S. aureus* and a *P. aeruginosa* extoxin A, and present

claims 31-33 are directed to *S. aureus*. Each of the secondary references describes a polysaccharide conjugated to a protein other than rARU.

There is no motivation to combine the references. Specifically, none of the secondary references mentions rARU, and thus no motivation is provided to use rARU with each of the polysaccharides disclosed in the secondary references, much less use rARU with a composition formulated for injection as claimed. Similarly, none of the secondary references mention that the disclosed polysaccharide can be substituted for Thomas' protein antigens.

Surprisingly, the Examiner suggests that the combination of references was made without the requisite motivation to select a particular species. For example, the Examiner alleges on page 8 of the Advisory Action mailed November 26, 2002 that

> it would have been obvious to couple the *C. difficile* toxin as taught by Thomas Jr. et al to the serotype *14 Streptococcus pneumoniae* (*i.e.* antigen) of Schneerson et al because Thomas Jr. et al teach that <u>any</u> antigen to which a protective and/or therapeutic immune response is desired may be administered with an adjuvant of this invention (emphasis in original).

The Examiner has made identical comments with respect to Taylor's disclosure of *Shigella*, with respect to Devi's disclosure of *E. coli* and *N. meningitides*, and with respect to Fattom's disclosure of *S. aureus* (please see pages 11, 15, and 18 of the Advisory Action). Combining the secondary references' polysaccharide antigen species based on the mere motivation of selecting "any" antigen in Thomas, without more specific motivation, is a departure from the present caselaw as outlined above.

As such, it is respectfully submitted that *prima facie* obviousness has not been established for any cited combination of references, and thus, reversal of this rejection also is respectfully requested.

9. Appendix

An Appendix containing a copy of the claims as currently pending is attached.

The Assistant Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.17 that may be required by this Brief, or to credit any overpayment, to Deposit Account No. 03-1952.

Respectfully submitted,

Dated: April 10, 2003 By: _____

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APPENDIX

1. An immunogenic composition for eliciting an immune response to a pathogenic organism which composition comprises a recombinant protein and a polysaccharide component, wherein said protein comprises the toxin A repeating units (*r*ARU) of *Clostridium difficile* and said polysaccharide component is characteristic of a pathogenic microorganism, which pathogenic microorganism is other than *C. difficile*,

wherein said composition is formulated for injection.

3. The immunogenic composition of claim 1, wherein said polysaccharide component is a capsular polysaccharide or a lipopolysaccharide.

6. The immunogenic composition of claim 1, wherein said protein is a fusion protein.

13. The immunogenic composition of claim 1, wherein said immune response comprises a cellular immune response.

14. The immunogenic composition of claim 1, wherein said immune response comprises a humoral immune response.

15. The immunogenic composition of claim 1, wherein said immune response is protective against said pathogenic microorganism.

19. The immunogenic composition of claim 1, wherein said polysaccharide has been isolated from said pathogenic microorganism.

20. The immunogenic composition of claim 1, wherein said pathogenic microorganism is selected from the group consisting of: *Streptococcus pneumoniae*; *Neisseria meningitidis*; *Escherichia coli*; and *Shigella.*

23. The immunogenic composition of claim 20, wherein said pathogenic microorganism is *Streptococcus pneumoniae*.

24. The immunogenic composition of claim 23, wherein said immune response is protective against *Streptococcus pneumoniae*.

25. The immunogenic composition of claim 20, wherein said pathogenic microorganism is *Shigella*.

26. The immunogenic composition of claim 25, wherein said immune response is protective against *Shigella*.

28. The immunogenic composition of claim 20, wherein said pathogenic microorganism is *Neisseria meningitidis*.

29. The immunogenic composition of claim 20, wherein said pathogenic microorganism is *Escherichia coli* K1.

30. The immunogenic composition of claim 1, wherein said pathogenic microorganism is selected from the group consisting of: *Staphylococcus aureus*; coagulase-negative *Staphylococcus*; *Enterococcus* species; *Enterobacter* species; *Candida* species; and *Pseudomonas* species.

31. The immunogenic composition of claim 30, wherein said immune response is protective with respect to *Staphylococcus aureus*; coagulase-negative *Staphylococcus*; *Enterococcus* species; *Enterobacter* species; *Candida* species; or *Pseudomonas* species.

33. The immunogenic composition of claim 30, wherein said pathogenic microorganism is *Staphylococcus aureus* serogroup 5 or serogroup 8.

36. The immunogenic composition of claim 1 which further comprises a pharmaceutically acceptable carrier.

37. A vaccine comprising the immunogenic composition of claim 36.

38. The vaccine of claim 37, wherein said vaccine is formulated for use in humans.

39. The vaccine of claim 37, wherein said vaccine is formulated for use in animals.

62. The immunogenic composition of claim 28, wherein said immune response is protective against *Neisseria meningitidis*.

63. The immunogenic composition of claim 1, wherein said polysaccharide component is covalently coupled to said protein.

64. (Withdrawn) A method to elicit an immune response in a subject to a pathogenic organism which method comprises injecting a subject in need of such response with an effective amount of the immunogenic composition of claim 1.

65. (Withdrawn) A method to elicit an immune response in a subject to a pathogenic organism which method comprises injecting a subject in need of such response with an effective amount of the immunogenic composition of claim 36.

66. (Withdrawn) A method to elicit an immune response in a subject to a pathogenic organism which method comprises injecting a subject in need of such response with an effective amount of the vaccine of claim 37.